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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/568,628	09/05/2006	Hirohiko Hohjoh	U 016154-7	2748

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EXAMINER	
CHONG, KIMBERLY	
ART UNIT	PAPER NUMBER
1635	

NOTIFICATION DATE	DELIVERY MODE
09/22/2011	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/568,628	HOHJOH, HIROHIKO	
	Examiner	Art Unit	
	KIMBERLY CHONG	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 June 2011*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

5)☒ Claim(s) *claims 1-5, 9-18 and 22-28* is/are pending in the application.

5a) Of the above claim(s) *24,25,27 and 28* is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1-5,9-18,22,23 and 26* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

12)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application/Amendment/Claims

Applicant's response filed 06/23/2011 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 12/28/2010 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

With entry of the amendment filed 06/23/2011, claims 1-5, 9-18 and 22-28 are pending, claims 24-25 and 27-28 are withdrawn and claims 1-5, 9-18, 22-23 and 26 are currently under examination.

New Claim Objections and Rejections

Necessitated by claim amendments

Claim Objections

Claim 4 is objected to because of the following informalities: the limitation "one additional nucleotide located position 11-13..." appears to be missing some phrasing between the words located and position such as "at" for example. This phrasing is a suggestion and as a reminder to Applicant, any claim amendment must have support in the instant specification.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 4 and 17 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection which is necessitated by new claim amendments.

The claims recite the limitation such that the dsRNA of claims 1 and 11, from which they depend, has "one additional nucleotide located" at positions 11-13 that has a mismatched nucleotide. Applicant points to support for these claim amendments very generally as found "throughout the specification". A cursory look through the specification does not yield adequate support for a dsRNA wherein two nucleotides are mismatched at positions 11-13. The paragraphs from the specification are reproduced below which disclose only one mismatched nucleotide at positions 11-13. The language of "one additional" is in reference to the dsRNA have in addition to mismatched nucleotides between the ends *as well as one additional mismatch at positions 11-13*, preferably at position 12.

> [0029] In order to efficiently suppress the expression of the target gene in the cell, in addition to the abovementioned mismatch at the 3'-end of the sense strand, **it is advantageous to introduce a mismatch in one nucleotide located at position 11-13 from its 3'-end**. Therefore, in a preferred embodiment of the present invention, the **double-stranded RNA molecule according to the first aspect of the present invention is designed such that one additional nucleotide located at position 11-13, more preferably at position 12**, from the 3'-end of the sense strand of the double-stranded part is not complementary to the antisense strand. [emphasis added]
>
> [0030] It has been confirmed by the experimental data using a double-stranded RNA molecule in which mismatches are introduced in two nucleotides at the 3'-end and in one nucleotide at position 12 from the 3'-end in a 19-20 nucleotide long sense strand, **that the double-stranded RNA molecule having a mismatch in one nucleotide located at position 11-13 from the 3'-end of the sense strand of the double-stranded part is advantageous in enhancing the effect on suppressing the gene expression**. Further, the site of this mismatch is close to the cleavage site of the target gene transcription product by RISC. Therefore, in the double-stranded RNA molecule according to the first aspect of the present invention, in addition to the mismatches at the 3'-end of the double-stranded part of the sense strand, a mismatch may be introduced in one nucleotide located at nucleotide position 1-3 in 5'- or 3'-direction from a site on the sense strand of the double-stranded part, the site corresponding to the cleavage site of the target gene transcription product by RISC. The cleavage site of the target gene transcription product by RISC can be determined by those skilled in the art according to the sequence in the specific region of the target gene contained in the double-stranded RNA molecule; however, it is typically in the central part of the sequence of the abovementioned specific region. [emphasis added]

If Applicant believes that such support is present in the specification and claimed priority documents, Applicant should point, with particularity to a page, paragraph and line number, to where such support is to be found.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-5, 9-18, 22-23 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zamore et al. (US 2005/0186586 cited on PTO Form 892 mailed 01/24/2008), Jayasena et al. (US 20040248299 cited on PTO Form 892 mailed 11/13/2008), Khvorova et al. (Cell, Vol. 115: 209-216, 2003) Elbashir et al. (EMBO Journal 2001, Vol. 20, No. 23: 6877-6888 of record cited on PTO Form 892 mailed 10/04/2007), Hamada et al. (Antisense and Nucleic Acid Developments 12: 301-309, 2002 of record cited on IDS filed 09/03/2009) and Davidson et al. (US 2004/0241854).

The claims are drawn to a double stranded RNA (dsRNA) molecule capable of suppressing the expression of a target gene in a cell by RNAi, which is improved as compared to a conventional siRNA, wherein one or more nucleotides in order from the 3' end of the sense strand is not complementary and/or one or more nucleotides in order from the 5' end of the sense strand of the double stranded part of the molecule are not complementary to the antisense strand and wherein one and an additional nucleotide located at position 11-13 from the 3' end of the sense strand is not complementary to the antisense strand, wherein the dsRNA does not induce double stranded protein kinase in a cell, wherein the dsRNA has a strand length of 29 nucleotides or less and drawn to dsRNA wherein either the 5' end of the antisense or the 5' end of the sense strand are guided into the RISC.

Please note: The sense strand is defined in the specification as being homologous to the target gene. Thus any prior art which teach a mismatch in the

antisense strand as compared to the target gene would also be interpreted such that the mismatch is also between the sense strand since the sense strand is homologous to the target gene. Further the claims are not drawn to any particular nucleotide sequence, therefore as stated above a mismatch introduced in the antisense strand would meet the limitations of the claims.

Zamore et al. teach dsRNA having mismatch nucleotides between the sense and antisense strands at both the 3' and 5' ends (see Figures 14, 17 and 21) and found that dsRNA with mismatched ends were more efficient that conventional completely complementary dsRNA (see at least Figure 14b and the specification for detailed explanation). Zamore et al. refers to the antisense strand as being the guide strand that is complementary to the target sequence and is capable of being loaded into the RISC complex (see paragraph 0088). Zamore et al. teach dsRNA with mismatched nucleotides between the sense and the antisense strands, particularly at nucleotides 9-12) were still able to bind with RISC thereby demonstrating the dsRNA can tolerate mismatched nucleotides in the center (see at least Figure 17b). Zamore et al. teach the dsRNA with mismatched nucleotides allowed more specificity of the guide antisense strand to enter RISC thereby increasing RNAi activity.

Jayasena et al. teach dsRNA that are capable of mediating sequence specific gene silencing which play a significant role in understanding gene function, signal transduction pathways and identifying therapeutic agents in the future (see page 8). Jayasena et al. teach dsRNA duplexes cleaved into duplexes having strands of 21-25 nucleotides in length (see pages 1-2 and Figure 1). Jayesena et al. recognized that

siRNA duplexes wherein the duplex in the middle has higher stability and the ends of each strand were more weakly associated were more capable of entering the RISC complex (see pages 21-22).

Likewise Khvorova et al. (along with Jayasena as co-author) teach efficient siRNA capable of unwinding and loading into the RISC require low internal binding of the first four nucleotides on the antisense strand (see at least pages 211-212). Khvorova et al. further found that siRNA molecules were more functional that had mismatched nucleotides, or low internal stability, at positions 9-14 counting from the 5' end of the antisense strand and state that because the target mRNA is cleaved between position 9-10 from the 5'end of the antisense strand, additional flexibility in this region is important for target cleavage. Khvorova et al. therefore provide motivation to incorporate mismatches in this area on either side of the cleavage position to increase target cleavage.

Hamada et al. demonstrates mismatched nucleotides between the sense and antisense strands of a dsRNA are well tolerated with respect to position 11 from the 3' end of the sense strand and further demonstrate dsRNA with no more than one or two mismatched nucleotides having the best silencing activity (see at least page 306).

Moreover, Davidson et al. teach a dsRNA with a mismatched nucleotide at position 9, 10 and 11 of the antisense strand as compared to the target RNA was capable of allele-specific gene silencing, thus being very efficient at silencing mutant target genes as compared to wild type genes.

It would have been obvious for one of skill in the art to make a dsRNA with mismatched nucleotides between both the 3'and 5' end end of the sense and 5' and 3' end of the antisense strand to increase the efficiency of antisense guide strand to mediate RNAi. It would have further been obvious to one of ordinary skill in the art to make the dsRNA with mismatched nucleotides in the center region to increase the efficiency of RNAi.

As shown by Zamore, Jayasena and Khvorova et al., mismatched nucleotides on the ends of the duplex region of the dsRNA allows for each strand to be more weakly associated such that the antisense guide strand can unwind from the sense strand and load into RISC and mediate RNAi more efficiently. Zamore et al. demonstrates a dsRNA with up to 4 nucleotide mismatched nucleotides starting from the 3' end of the sense strand wherein this dsRNA was more efficient as compared to a fully complementary dsRNA (see at least Figure 14). Zamore et al. further demonstrates dsRNA that are capable of efficient gene silencing wherein the dsRNA has mismatched nucleotides on each end as well as demonstrating dsRNA wherein the center nucleotides are mismatched.

The benefits of a decreased base-pair strength at the terminal end and mismatched nucleotides at the cleavage site was well recognized in the prior art at the in the early studies of siRNA. Elbashir et al. recognized that siRNA duplexes with less base-pair strength at the 5' end of the strand of the duplex that was complementary to the target mRNA was able to act as a guide strand in mediating RNAi and was more permissive for mismatched target mRNA recognition (see Figure 1 and page 6885).

Elbashir et al. further teach the position of target RNA cleavage site is located in the center of a siRNA duplex region which is 11 or 12 nucleotides downstream of the first nucleotide in the duplex region (see page 6882). Elbashir et al. recognized that the nucleotides in the duplex region of the siRNA that were opposite the cleavage site of the target RNA are important specificity determinants and even a single nucleotide change can reduce RNAi activity. Elbashir et al. teach such siRNA are able to discriminate mutant alleles and therefore designing siRNA that have mismatches in the center of the duplex region that can discriminate between wild-type and mutant alleles can be used in therapeutic applications (see page 6885).

As taught by Khvorova, one of skill in the art would have clearly been motivated to incorporate mismatched nucleotides in the center of the duplex region near the cleavage site as this provides additional flexibility for the dsRNA and improves gene silencing by the molecule. When deciding on where specifically to place this mismatched nucleotide in the center region, the skilled artisan would have looked to Hamada et al. who demonstrates dsRNA with mismatched nucleotides at position 11 from the 3' end of the sense strand were more efficient that dsRNA with mismatched nucleotides comprising more than two nucleotides and outside the claimed region.

Moreover, one of skill in the art would have further been motivated to make a dsRNA with mismatched nucleotides in the center region, at least counting from position 11 from the 3' end of the sense region, given Davidson et al. teach in doing this, the dsRNA can discriminate between wild-type and mutant alleles. Davidson et al. provide the motivation to make this dsRNA with center mismatched nucleotides in order to study

the ability of a dsRNA to target a mutant target gene and decrease gene silencing in efforts to find a therapeutic agent for treatment of diseases resulting from mutant target genes. One would have expected to be able to incorporate mismatches at or near the cleavage site and would have been expected to be able to find the optimal position of mismatches in the central region of the duplex given both Elbashir et al., Khvorova et al and Hamada et al. teach methods of positioning the mismatches in a duplex in the center region allows for RNAi to occur and increased gene silencing ability.

Thus in the absence of evidence to the contrary, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Although this is a new grounds of rejection above, response to Applicant's argument is warranted as some of the same references are used in the above rejection.

First just to clarify the newly amended claims, Applicant states the claims are drawn to dsRNA wherein one or more mismatched nucleotides are at the 3' and 5' end of the sense strand "and/or" a mismatch is at position 11-13 of the double stranded part. The mismatch at position 11-13 is not optional and there is not language in the amended claims to indicate this mismatch is optional at this position.

Applicant argues Zamore et al. disclose dsRNA consisting of miRNA and these are distinguished from siRNA as the dsRNA are not capable of suppressing gene expression by RNAi and are generated by Dicer.

In response, the claims are drawn to dsRNA and do not recite the dsRNA is in fact siRNA and even if the claims defined dsRNA to be a siRNA, the dsRNA taught by Zamore et al. would still meet the claimed limitation as they are shown throughout the specification to be capable of reducing target gene expression. Moreover, the claims do not recite how the dsRNA is processed, either by Dicer or other means, and thus the dsRNA taught by Zamore et al. meets the claim limitations.

Further as stated above, the sense strand is defined in the specification as being homologous to the target gene. Thus any prior art which teach a mismatch in the antisense strand as compared to the target gene would also be interpreted such that the mismatch is also between the sense strand since the sense strand is homologous to the target gene. Further the claims are not drawn to any particular nucleotide sequence, therefore as stated above a mismatch introduced in the antisense strand would meet the limitations of the claims.

Response to Arguments

Claim Rejections - 35 USC § 102

The rejection of claims 1-5, 9-18, 22-23 and 26 under 35 U.S.C. 102(e) as being anticipated by Zamore et al. (US 2005/0186586 cited on PTO Form 892 mailed 01/24/2008) as evidenced by Aravin et al. (Developmental Cell, 2003 cited on PTO Form 892 mailed 01/24/2008) and Elbashir et al. (Nature 2001 cited on PTO Form 892 mailed 01/24/2008) is withdrawn. An argument to this rejection is moot except for the points discussed above.

Claim Rejections - 35 USC § 103 - maintained

The rejection of claims 1-5, 9-18, 22-23 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jayasena et al. (US 20040248299), Khvorova et al. (US 2007/0031844), Elbashir et al. (EMBO Journal 2001, Vol. 20, No. 23: 6877-6888) and Holen et al. (Nucleic Acids Research 2002, Vol. 30, No. 8: 1757-1766) is withdrawn. An argument to this rejection is moot except for the points discussed above.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to KIMBERLY CHONG whose telephone number is 571-272-3111. The examiner can normally be reached Monday thru Thursday between 6 and 3 pm.

If attempts to reach the examiner by telephone are unsuccessful please contact the SPE for 1635 Heather Calamita at 571-272-2876. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public. For more information about the PAIR system, see http://pair-direct.uspto.gov.

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